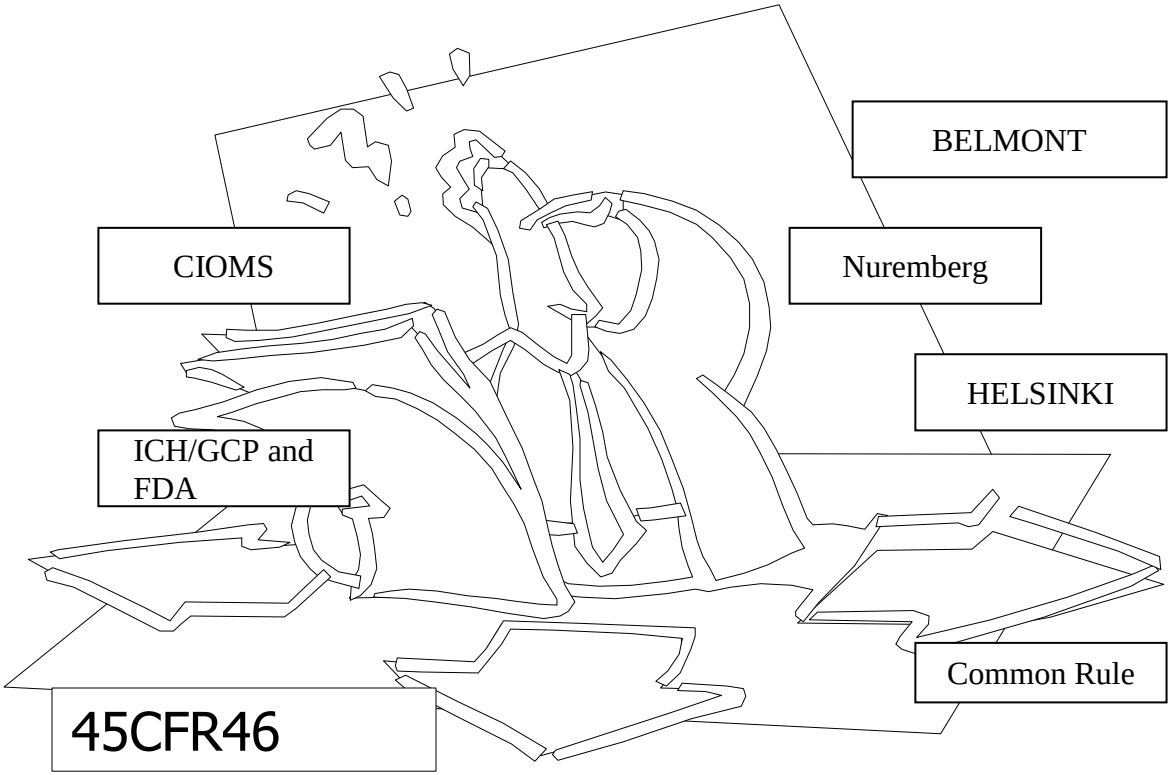
DO THE CODES APPLY TO MY RESEARCH?



Codes of Research Ethics

- The Nuremberg Code
- The Declaration Of Helsinki
- The Belmont Report
- CIOMS/WHO International Ethical Guidelines For Biomedical Research Involving Human Subjects
- ICH/GCP-International Conference on Harmonization- Good Clinical Practice

How are codes and guidelines to be used?

- Aspirations, fundamental principles or rules?
- Universal?
- Absolute or subject to revision and interpretation?

U.S. Federal Regulations and Guidelines

- Title 45 US CFR.46
  - The Common Rule
  - Additional subparts
- NIH Policy and Guidelines on women, ethnic minorities and children
- 21 CFR. 50 AND 56- FDA Regulations
- NIH FWA

US Federal Regulations

- Who is required to follow the federal regulations?
- Interpretation of the federal regulations?

- Research ethics are broader and deeper than any actual or possible regulations or codes could encompass

Nuremberg Code 1947

- Nazi doctor's trial
- In response to 'experiments' done with prisoners in concentration camps
- Authors were American
- 10 principles

Nuremberg Code 1947

- 1. The voluntary consent of the human subject is absolutely essential

- 2. The experiment should be such as to yield fruitful results for the good of society unprocurable by other means… and not random and unnecessary in nature

Declaration Of Helsinki

- World Medical Association
- By physicians for physicians
- A "living" document revised multiple times (1964, 75, 83, 89, 96, 2000)
- http://www.wma.net

Declaration Of Helsinki

- "WMA has prepared the following recommendations as a guide to every physician in biomedical research*…standards as drafted are only a guide to physicians all over the world."* (1983, 1989, 1996)

- WMA has developed the Declaration... as a *statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects*" (2000)

Declaration Of Helsinki

(pre-2000)

- Therapeutic versus non-therapeutic research

- Independent review of the "Design and performance of each experimental procedure-clearly formulated in a specific protocol"

Declaration Of Helsinki

pre-2000 contributions

- Explicitly allowed permission from a legal guardian

- Research not in accordance with Helsinki principles should not be accepted for publication.

Declaration Of Helsinki 2000

- Greatly expanded
- Change in structure
- Controversy, esp.
  - #29- use of placebos
  - #30- obligations for treatment post-trial

Declaration of Helsinki (2000)

- The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. *This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, and therapeutic method exists* (#29)

Declaration of Helsinki
clarification 2002

- Reaffirmed essence of #29

- Allowed for ethically acceptable exceptions:
  - compelling and scientifically sound methodological reasons
  - minor condition and no additional risk of serious or irreversible harm

Declaration Of Helsinki
(2000)

- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study (#30)

Declaration of Helsinki clarification 2004

- "The WMA reaffirms … that it is necessary during study planning process to identify post-trial access by study participants to prophylactic, diagnostic, or therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee can consider [them]…"

The Belmont Report

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979

- Boundaries between research and practice
- Ethical principles underlying the conduct of research:
  - Respect for persons
  - Beneficence
  - Justice

Respect For Persons

- Individuals should be treated as autonomous agents (capable of self-determination)
- Persons with diminished autonomy deserve protection

- **Application:** Informed consent

Beneficence

- Two general complementary rules:
  - Do not harm
  - Maximize possible benefits and minimize possible harms

- **Application**: Risk/Benefit assessment

Justice

- Fairness in the distribution of the benefits and burdens of research (distributive justice)

- **Application:**
  - Fair procedures and outcomes in the selection of subjects

International Ethical Guidelines- CIOMS

- Council for International Organizations of Medical Sciences (CIOMS)/WHO)

- Application of the Declaration of Helsinki in developing countries

  - http://www.cioms.ch/

CIOMS guidelines

- Ethical review of epidemiological studies 1991, currently under revision
- International Ethical Guidelines for Biomedical Research Involving Human Subjects 1993, 2002

CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)

- 21 Guidelines with extensive commentary
- 2002 additions:
  - Ethical justification and scientific validity (#1)
  - Benefits and Risks (#8)
  - Limitations on risk for those who cannot consent (#9)
  - Choice of controls (#11)
  - Strengthening capacity (#20)
  - Obligation of external sponsors for health care services (#21)

CIOMS International Ethical Guidelines

- Responsiveness to the health needs and priorities of the community
- 'Reasonable availability'
- Rights of subjects to compensation for research injury

ICH

- "The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)… brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration."
  - http://www.ich.org/cache/compo/276-254-1.html

ICH

- "The objective … is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health."

ICH Harmonised Tripartite Guideline-GCP (E6-(R1) 1996)

- Objective: "…to provide a unified standard ….for mutual acceptance of clinical data by regulatory authorities in those jurisdictions"

- GCP-"…an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects"

ICH-Guideline for Good Clinical Practice

- "Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical data are credible" (ICH-E6)

- Adopted by US FDA as Good Clinical Practice: Consolidated Guideline (1997)
- http://www.ich.org

45CFR.46 Protection of Human Subjects

- PHS policy 1966
- National Research Act (1974)
- DHEW regulations (1981)
- The Common rule- 17 Federal agencies, including DHHS (1991)

45CFR.46 Protection of Human Subjects

- Composition and function of a local institutional review board (IRB)
- Requirements for informed consent
- IRB to assure that:
  - risks are minimized,
  - research risks are reasonable in relation to expected benefits,
  - subject selection is equitable, and
  - informed consent will be obtained from each subject.

45CFR 46

- Subpart B- Fetuses, pregnant women, and human *in vitro* fertilization
- Subpart C- Prisoners as subjects
- Subpart D- Children
- ?future subparts?

NIH guidelines on the inclusion of women and minorities

- NIH Reauthorization Act (1993).
- Women and members of ethnic minority groups are to be included (some exceptions)
- Outreach programs for recruitment
- Sufficient to provide for a valid analysis of differences between groups

NIH Policy and Guidelines on the Inclusion of Children as Participants in Research

"…children must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them…" (Effective October 1, 1998)

Assurance of Compliance with Federal Regulations

- Office of Human Research Protections (OHRP) http://www.hhs.gov/ohrp
- Assurance (FWA)
- Intramural Office of Human Subjects Research http://ohsr.od.nih.gov/

FDA REGULATIONS

- 21CFR.50 Protection of Human Subjects (informed consent)
  - Subpart D on research with children
- 21CFR.56 IRB composition and function
- Some differences from the common rule.

FDA REGULATIONS

- Part 54-Financial disclosure
- Part 312- IND applications
- Part 314- new drug applications
- Guidance and information sheets
- http://www.fda.gov/oc/gcp

Which rules?

- NIH-funded investigator conducting a randomized, placebo controlled study of a new drug for arthritis. She intends to publish the results.

- What rules should she follow?

So, which rules and guidance should I follow?

- For *federally funded* research: 45 CFR.46, subpart A or the Common Rule

- For *NIH funded* research- 45 CFR.46, Subparts A through D; and NIH guidelines

So, which rules and guidance should I follow?

- For research testing a *drug, biologic, or device* that will ultimately be submitted for FDA approval- 21 CFR. 50 and 56 and ICH/GCP

- If above trials are *funded by NIH-* also 45 CFR.46 and NIH guidelines

So, which rules and guidance should I follow?

- If you want to publish your research in a major medical journal- Declaration of Helsinki

So, which rules and guidance should I follow?

- For international research:
  - The legal and ethical requirements of the host jurisdiction
  - CIOMS guidelines and Helsinki
  - If NIH funded- 45 CFR.46

ALPHABET SOUP

- CIOMS
- FWA
- OHRP
- 45CFR46
- ICH
- OHSR
- IRB